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Histamine and neuroinflammation: insights from murine experimental autoimmune encephalomyelitis

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Multiple sclerosis (MS) is a chronic inflammatory, neurodegenerative disease of the CNS whose pathogenesis remains largely unknown, and available therapies are rarely successful in reversing neurological deficits or stopping disease progression. Ongoing studies on MS and the widely used murine model of experimental autoimmune encephalomyelitis (EAE) are focused on the many components of this complex and heterogeneous neurodegenerative disease in the hope of providing a mechanism-based characterization of MS that will afford successful strategies to limit and repair the neuronal damage. Recently, histamine has been postulated to have a key regulatory role in EAE and MS pathogenesis. Histamine is a mediator of inflammation and immune responses, exerting its many actions through four G protein-coupled receptors ($H_{1,2,3,4}R$) that signal through distinct intracellular pathways and have different therapeutic potentials as they vary in expression, isoform distribution, signaling properties, and function. Immune cells involved in MS/EAE, including dendritic cells (DCs) and T lymphocytes, express H_1R, H_2R and H_4R, and histamine may have varying and counteracting effects on a particular cell type, depending on the receptor subtypes being activated. Here, we review evidence of the complex and controversial role of histamine in the pathogenesis of MS and EAE and evaluate the therapeutic potential of histaminergic ligands in the treatment of autoimmune diseases.

Keywords: multiple sclerosis, EAE, autoimmune diseases, H_1 receptor, H_2 receptor, H_4 receptor

MS: A COMMON INFLAMMATORY-DEGENERATIVE CNS DISEASE

Multiple sclerosis (MS) is the most common, non-traumatic cause of neurological disability among young adults in Western Europe and North America. The current hypothesis asserts that MS is triggered by environmental factors in individuals with complex genetic-risk profiles. As with other autoimmune diseases, MS shows moderate polygenic inheritability and may be caused or exacerbated by environmental exposure such as viral infections or vitamin D deficiency (Correale et al., 2009). It is characterized by clinical and genetic heterogeneity and with individuals with MHC class II complex genes being most susceptible (Ballerini et al., 2004; Gourraud et al., 2011). Out of the MHC locus a plethora of genes have been described as minor contributors to genetic risk, among which are those encoding for IL-2 receptors and IFN-γ (Blankenhorn et al., 2011).

MS is characterized by inflammation of the central nervous system (CNS) in which focal lymphocytic infiltrations lead to damage of myelin and axons associated with neurological dysfunction. Initially, the inflammatory response is transient and remyelination occurs, but this is not durable and over time widespread microglial activation ensues along with extensive and chronic neurodegeneration.

The observation that histamine may be implicated in MS dates back to the early 1980s when Tuomisto et al. (1983) showed that patients with remitting or progressive disease have histamine levels about 60% higher than controls. Another clinical study, though, did not show elevated concentrations of histamine and its metabolite methylhistamine in MS patients when compared, in this case, with individuals affected by other neurological diseases (Rozniecki et al., 1995). More recently, gene-microarray analysis has shown that histamine H_1 receptor (H_1R) expression is upregulated in MS lesions (Lock et al., 2002), and epidemiological studies suggest a protective effect of brain penetrating H_1R antagonists (Alonso et al., 2006). Furthermore, in a small pilot study, a cohort of MS patients treated with an H_1R antagonist showed signs of neurological amelioration (Logothetis et al., 2005). The H_1R has long been associated with inflammatory responses and for decades, the antiallergic and antiinflammatory activities of H_1R antagonists have been used in therapy. Possible explanations of the therapeutic potential of H_1R antagonists come from preclinical results in experimental allergic encephalomyelitis (EAE) in mice.

Abbreviations: APCs, antigen presenting cells; BBB, blood brain barrier; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; HDC, histidine decarboxylase; MOG_{35-55}, Myelin Oligodendrocyte Glycoprotein; MS, multiple sclerosis; $PLP_{139-151}$, myelin proteolipid protein.

EAE IS A GOOD MODEL FOR STUDYING MS

Pathological features of MS are studied in three main animal models: toxic induction of disease, viral induction, and several types of EAE. Cuprizone and lysolecithine, for example, are used to investigate demyelination and remyelination in the CNS (reviewed in Woodruff and Franklin, 1999; Kipp et al., 2009), and to investigate how viral infections can induce CNS autoimmunity; Theiler's murine encephalomyelitis virus (TMEV) inoculated intracerebrally is a currently used experimental protocol (Olson et al., 2001). EAE may be actively induced by immunization of susceptible mouse strains with myelin proteins or myelin protein immunodominant peptides in the presence of complete Freund's adjuvant (CFA), or may be passively induced by transfer of myelin specific T cells. EAE, in most animal models, is mainly driven by MHC class II restricted, autoimmune $CD4^+$ T cells and the clinical course depends on the immunization protocol, as not all combinations of genetic background, antigen, and adjuvant induce EAE. Classically, EAE immunized animals develop an ascending flaccid paralysis from tail to head with variable disease score; manifestation of clinical symptoms may be relapsing remitting, monophasic, or chronic. In active disease pathogenesis of EAE, two main steps are usually described: priming of myelin-reactive T cells and CNS invasion through the blood brain barrier (BBB). Once cells invade the CNS, local, and infiltrated antigen presenting cells (APCs) will present myelin peptides for full activation. Many different types of cells contribute to the development of the disease: APCs, mainly dendritic cells (DCs), B cells, microglia, macrophages, and astrocytes, although astrocytes have an unclear function in EAE development (Volterra and Meldolesi, 2005).

For many years the principal paradigm of EAE pathogenesis has been centered on IFN-γ producing T cells (Th1). These cells differentiate upon exposure to IL-12 and IFN-γ, are characterized by transcription factors T-bet, STAT1, STAT4 and are found as infiltrates in CNS lesions. With time this paradigm has been partially revised and a recently described T cell subpopulation has been shown to have a central role in disease pathology: Th17 cells that differentiate in the presence of IL-6 and TGF-β and need RORγt as a transcription factor (Gutcher and Becher, 2007). Th17 cells have been extensively studied in several autoimmune diseases and there is wide agreement on the instability of the phenotype that may switch between Th1 and Th17. This plasticity derives from epigenetic factors with Th17-derived Th1 cells promoting autoimmune diseases (Annunziato et al., 2007; Mukasa et al., 2010). Altogether, the studies on $CD4^+$ T cells involved in EAE do not ascribe a particular role to one specific T cell population, and T helper cells may undergo alterations. Furthermore, recent observations suggest that EAE can elicit both Th1 and Th2 immune responses in the same subjects, i.e., elements of the Th2 cell-mediated allergic response are associated with autoimmune demyelination (Pedotti et al., 2003).

In conclusion, EAE has provided mechanistic insights into the complex pathogenesis of MS and has proven to be a good model for the preclinical testing of new diagnostic or treatment modalities. In addition, it is considered a well-suited model because of its histopathological and immunological similarities to MS (Schreiner et al., 2009). Consequently, the large majority of studies looking for a possible implication of histamine in autoimmune diseases have been performed using the murine EAE experimental model.

HISTAMINE IN AUTOIMMUNE DISEASES

Histamine has long been known to be a major promoter of allergic inflammatory conditions and gastric acid secretion. Synthesized by histidine decarboxylase (HDC) from histidine, histamine was later described as a neurotransmitter in the CNS that regulates several physiological processes and homeostatic functions including cognition, arousal, circadian, and feeding rhythms (Haas et al., 2008). These effects are mediated through four distinct G protein-coupled receptors (H_1R, H_2R, H_3R, and H_4R) with very low sequence homology. The H_1R couples to G_q proteins, leading to phospholipase C activation and calcium mobilization (Bakker et al., 2002). The H_2R activates $G\alpha_s$ and increases camp formation, whereas the H_3R mediates its function through $G\alpha_{i/o}$, inhibits cAMP synthesis (Bakker et al., 2002), activates MAP kinases and the AKT/GSK3β axis (Bongers et al., 2007; Mariottini et al., 2009).

Inflammatory responses consequent to histamine release have long been thought to be mediated by the H_1R, and antihistamines commonly used to treat allergies are H_1R antagonists. The discovery of a fourth histamine receptor (H_4R) and its expression on virtually all inflammatory and immune cells, though, has prompted a reassessment of the role of histamine in inflammatory and immune disorders and widened the spectrum of potential therapeutic interventions (Thurmond et al., 2008). The H_4R is coupled to $G\alpha_{i/o}$ proteins (Liu et al., 2001) and to the β-arrestin pathway (Rosethorne and Charlton, 2011), and signals via intracellular increases of calcium. Its functions include mediation of calcium mobilization, shape change, actin polymerization (Barnard et al., 2008) chemotaxis of mast cells, and eosinophils (Buckland et al., 2003), and up-regulation of adhesion molecules (Buckland et al., 2003).

All histamine receptors are expressed on the complement of cells involved in autoimmune diseases, with the exception of the H_3R that is normally not expressed by hematopoietic cells, but is mostly confined to the CNS (Passani et al., 2011b). Histamine participates in the development and progression of EAE as it controls accessibility to the site of inflammation by modulating vasopermeability and adhesion molecule expression, chemotaxis, and the cytokine profile of DCs and T lymphocytes, the main players in autoimmune diseases.

ROLE OF HISTAMINE RECEPTORS IN EAE: CONTROVERSIAL RESULTS

The regulatory functions of histamine relevant to the onset and progression of neuroinflammatory diseases and in particular EAE, are being studied in genetically modified mice lacking histaminergic receptors, and with relatively selective agonists and antagonists. Hence, the contribution of each histamine receptor in autoimmune diseases has been identified. Histamine plays a complex role with varying and counteracting effects, depending on the receptor subtypes being activated and the targeted tissue (see **Table 1**). *In vitro* experiments have shown that activation of H_1R and H_2R on DCs modulates cytokine and chemokine

Table 1 | Histamine receptors and EAE.

Histamine receptor	EAE	Investigated cell types	Pharmacological target	Disease outcome	Reference
H_1	SJL mice $PLP_{139–151}$	Increased H_1R expression on Th1 cells	H_1R antagonism	Less severe disease	Pedotti et al., 2003
		Humoral immunoresponses			El Behi et al., 2007
	$MOG_{35–55}$ H_1R-KO mice	$CD4^+$T cells		Reduced IFN-γ, increased IL-4 Less severe disease	Ma et al., 2002 Noubade et al., 2007
	$MOG_{35–55}$ H_1R-KO mice	Endothelial cells	H_1R overexpression	Restored BBB integrity Less severe disease	Lu et al., 2010
	$PLP_{139–151}$ SJL mice	$CD3^+$T cells	H_1R activation	Reduced IFN-γ Decreased endothelial adhesiveness	Lapilla et al., 2011
H_2	$MOG_{35–55}$ H_2R-KO mice	APC Th1		Reduced cytokines Inhibition of cell polarization Less severe disease	Teuscher et al., 2004
	$MOG_{35–55}$ C57/Bl6	Proinflammatory cells	H_2R activation	Less severe disease	Emerson et al., 2002
	$PLP_{139–151}$ SJL mice	$CD3^+$T cells	H_2R activation	Reduced IFN-γ Decreases endothelial adhesivness	Lapilla et al., 2011
H_3	$MOG_{35–55}$ H_3R-KO mice	Th1 Endothelial cells		Increased expression of chemokines/chemokine receptors BBB deregulation More severe disease	Teuscher et al., 2007
H_4	$MOG_{35–55}$ H_4R-KO mice	Treg		Lower frequency	del Rio et al., 2012
		Th17		Higher frequency More severe disease	
	$MOG_{35–55}$ C57/Bl6 mice	Th1 Mdc	H_4R antagonism	Increased IFN-γ, reduced IL-10 More severe disease	Passani et al., 2011a
	$MOG_{35–55}$ HDC KO mice	$CD3^+$T cells		Increased IFN-γ, TNF, More severe disease	Musio et al., 2006

APC, antigen presenting cells; BBB, blood brain barrier; mDC, myeloid dendritic cells; $MOG_{35–55}$, Myelin Oligodendrocyte Glycoprotein; $PLP_{139–151}$, Myelin Proteolipid Protein.

production and their ability to drive $CD4^+$ T-cell differentiation to the Th2 phenotype. On the other hand, H_4R activation modulates chemotaxis (reviewed in Schneider et al., 2010). Depending on the receptor engaged on polarized T cells, histamine can promote Th1 responses through H_1R and down-regulate both Th1 and Th2 responses through H_2R (Jutel et al., 2001). Similarly to DCs, H_1R and H_4R activation on $CD4^+$ T cells induces chemotaxis *in vitro*, whereas H_1R and H_2R modulate cytokine production (Schneider et al., 2010).

Mast cells are generally thought to be the major sources of histamine and can themselves be modulated by histamine as they express H_1R, H_2R, and H_4R. There is ample correlative and direct evidence that supports mast cell involvement in amplifying the severity of both MS and EAE. Mast cell-deficient W/W(v) mice exhibit significantly less severe disease than wild type littermates in both progressive (Sayed et al., 2011) and relapsing-remitting (Secor et al., 2000) models of EAE.

Susceptibility to EAE requires expression of *Hrh1*, the gene encoding the H_1R (Ma et al., 2002). The H_1R is expressed on Th1 cells in EAE mice brain lesions (Pedotti et al., 2003), where its presence is necessary for full encephalitogenic expression (Noubade et al., 2007). Furthermore, expression of the H_1R is up-regulated on encephalitogenic $PLP_{139–151}$ specific Th1 compared to Th2 cell lines (Pedotti et al., 2003). Not surprisingly, specific pharmacological targeting of H_1R results in amelioration of EAE (Pedotti et al., 2003; El Behi et al., 2007) and H_1R-deficient (H_1R-KO) mice exhibit a significant delay in the onset of EAE and a reduction in the severity of the clinical signs compared with WT mice (Ma et al., 2002; **Table 1**). In fact, $CD4^+$ T-cells from H_1R-KO mice produce significantly less IFN-γ and more IL-4 (that induces differentiation of naive $CD4^+$ T cells to Th2 cells) in *in vitro* assays compared to wild-type controls, indicating that H_1R signaling in $CD4^+$ T cells plays a central role in regulating pathogenic T-cell responses (Ma et al., 2002).

The H_2R also seems to partially regulate encephalitogenic Th1-cell responses and EAE susceptibility, as H_2R-KO mice develop a less severe disease than wild-type littermates during the acute, early phase (Teuscher et al., 2004). The failure of H_2R-KO mice to generate encephalitogenic Th1 effector cell responses is attributed to H_2R-mediated regulation of cytokine production by DCs that affects T-cell-polarizing activity. In conclusion, H_1R and H_2R seem to have a pro-inflammatory role and disease-promoting effect, but the story is not quite as simple as that, as H_1R or H_2R activation may also play an important role in limiting autoimmune responses.

Adhesion of T cells to the inflamed microcirculation precedes their penetration in the brain parenchyma, following breakdown of BBB integrity. H_1Rs are expressed on endothelial cells where they increase vascular permeability (Owen et al., 1980); however, functional expression of the H_1R on endothelial cells does not restore EAE susceptibility in H_1R-KO mice, rather, overexpression of the H_1R further suppresses the residual symptoms shown by H_1R-KO mice, suggesting that endothelial H_1R signaling is needed to maintain cerebrovascular integrity (Lu et al., 2010). Pedotti and colleagues (Lapilla et al., 2011) have demonstrated that histamine activating H_1R and H_2R, inhibits *in vitro* the proliferation of mouse $CD3^+$ T cells reactive against $PLP_{139–151}$, and their adhesiveness to the inflamed endothelium. Also, treatment with an H_2R agonist reduces the clinical signs of murine EAE (Emerson et al., 2002; **Table 1**). As pointed out by the authors (Pedotti et al., 2003; Lapilla et al., 2011) methodological differences may account for the discrepancies observed in *in vivo* and *ex vivo* experiments, such as the immunization protocols adopted. Also, *ex vivo* experiments may not necessarily recapitulate the integrated action of signals relevant to EAE and components of an integrated system maybe lost. On the other hand, genetically modified mice may carry alterations of systems other than the targeted ones, and activation of vicarious mechanisms may hinder the effects related to the deleted gene(s). In fact, the complete lack of HDC and histamine synthesis in HDC-KO mice exacerbates EAE and increases the production of proinflammatory cytokines (Musio et al., 2006). This phenotype does not seem to summarize the lack of signaling at histamine receptors observed in H_1R- and H_2R-deficient mice, rather a reduced effect of histamine at H_3R and H_4R (see below).

As mentioned earlier, H_3R are normally not expressed by hematopoietic cells, but are mostly confined to the CNS where they limit histamine synthesis and release (Arrang et al., 1983), as well as regulate other neurotransmitters' release (reviewed in Passani and Blandina, 2011). It was recently shown that deletion of the H_3R leads to more severe EAE, an effect associated with altered BBB permeability and an unexpected increased expression of chemokines/chemokine receptors that promote entry into the CNS on peripheral T cells that do not themselves express H_3R (Teuscher et al., 2007). The authors suggest that neuronal H_3R may serve as a central control of cerebrovascular tone, and negatively regulate susceptibility to neuroinflammatory diseases. Their proposed mechanism states that in H_3R-KO mice the absence of a presynaptic inhibition would lead to increased release of neurotransmitters and postsynaptic activity that would exert neurogenic control of BBB permeability and T cell chemokine profile.

THE COMPLEX ROLE OF H_4R DURING INFLAMMATORY RESPONSES IN EAE

The distribution of the H_4R on immune cells and its primary role in inflammatory functions has made it a very attractive target for the treatment of asthma and autoimmune diseases (Bhatt et al., 2010). Recent evidence has also shown the topological and functional localization of the H_4R in the CNS of both humans and rodents (Connelly et al., 2009; Strakhova et al., 2009). Immunohistochemical detection revealed that H_4Rs are expressed on the soma of sensory neurons with intense staining of small and medium diameter neurons, as well as lamina I-II of the lumbar spinal cord, where the immunoreactivity pattern suggests localization with terminals of primary afferent neurons (Connelly et al., 2009). These findings widen the range of therapeutic potentials of compounds targeting the H_4R, as antagonists might relieve itching by decreasing not only inflammation, but also the urge to scratch. The H_4R is detected on hematopoietic progenitor cells (Petit-Bertron et al., 2009), and its activation before exposure to growth factors leads to a drastic decrease in the percentage of cycling cells (Schneider et al., 2011). The H_4R expression is dynamic as it is up-regulated during the differentiation from human monocytes to DCs (Gutzmer et al., 2005). In addition, receptor levels may change with the progression of pathophysiological responses, e.g., inflammatory stimuli can up-regulate the expression of H_4R in monocytes (Dijkstra et al., 2007). The anti-inflammatory effect of H_4R antagonists in asthma and pruritus is consolidated (reviewed in Thurmond et al., 2008; Zampeli and Tiligada, 2009). The use of selective antagonists demonstrated a pro-inflammatory role for this receptor in several paradigms and suggested a facilitating action on autoimmune diseases (Jadidi-Niaragh and Mirshafiey, 2010). Furthermore H_4R are expressed on Th17 cells where their activation increases IL-17 production (Mommert et al., 2012). Quite surprisingly though, mice with a disrupted H_4R gene develop more severe EAE together with increased neuroinflammatory signs and increased BBB permeability compared to wild type mice (del Rio et al., 2012). In this paradigm, H_4R-KO mice have a lower frequency of infiltrating Treg cells that possess disease suppressive activity, more precisely during CNS invasion at day 10 post immunization (10 dpi), and a higher proportion of inflammatory Th17. Preliminary data in our laboratory are corroborating these findings (**Table 1**), as H_4R antagonists such as JNJ7777120 administered daily for eight days to EAE mice at the onset of clinical signs exacerbate the clinical and neuropathological signs of the disease (Passani et al., 2011a). In our model, a decreased release of regulatory cytokines such as IL-10 is accompanied with augmented production of IFN-γ in $MOG_{35–55}$-specific T cells during the acute phase of the disease (18–20 dpi), suggesting a more complex role of H_4R not only on regulatory mechanisms of the immune response but also on T effector cells.

In conclusion, the use of different inflammatory and immune models is producing conflicting results about the role of the H_4R in allergic and immune responses. For example, recent data show that the activation, and not antagonism, of H_4R leads to reduced pro-inflammatory capacity of a subpopulation of DCs found in inflamed tissues in atopic dermatitis (Gschwandtner et al., 2011). Also, in a murine model of allergic asthma, the administration

of H_4R agonists mitigated airway hyperreactivity and inflammation with a suggested direct effect on T regulatory cell recruitment (Morgan et al., 2007). It is clear that in the context of the conflicting activities of the H_4R that depend on its activation on different hematopoietic cells, additional research is needed to clarify whether H_4R agonists can yield promising drugs in the treatment of autoimmune diseases.

CONCLUSIONS

Histamine receptors play multiple roles in immune reactions and autoimmune disorders. Strategies aimed at interfering with the histamine axis may have relevance in the therapy of autoimmune diseases of the CNS as histamine may determine, through different receptor activation pathways, a shift in T helper cell subpopulation, may influence migration of lymphocytes and myeloid cells during CNS invasion, interfere with antigen presentation at the immune synapse level and finally, determine variations in normal neuronal functions. It will be of paramount importance to define the temporal sequence of histamine receptor activation during disease initiation in peripheral tissues and during CNS invasion. Hopefully, this will help the scientific community to put the sometimes confusing and contradictory observations reviewed here into better focus and provide a perspective for evaluating potential therapeutic interventions using histaminergic compounds.

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